Medical Science

To Cite:
Paduszyńska N, Dąbrowska A, Kruszewski A, Błaszczak K, Przybysz P, Szyszka M, Kucharska M. Therapeutic strategies in Uveal Melanoma: A comprehensive review of primary and metastatic disease treatment approaches. *Medical Science* 2024; 28: e68ms3370
doi: https://doi.org/10.54905/disssi.v28i149.e68ms3370

Authors' Affiliation:
[1]Dr Anna Gostynska Wolski Hospital, Independent Public Health Care Institution, Marcina Kasprzaka 17, 01-211 Warsaw, Poland
[2]University Clinical Centre of the Medical University of Warsaw, Banacha 1a, 02-097 Warsaw, Poland
[3]Regional Specialist Hospital in Ciechanów, Powstańców Wielkopolskich 2, 06-400 Ciechanów, Poland

*Corresponding Author
Dr Anna Gostynska Wolski Hospital, Independent Public Health Care Institution, Marcina Kasprzaka 17, 01-211 Warsaw,
Poland
Email: natalia_paduszynska@onet.eu

Contact List

Natalia Paduszyńska	natalia_paduszynska@onet.eu
Anna Dąbrowska	annaalicjadabrowska06@gmail.com
Adrian Kruszewski	adrkru7@gmail.com
Karolina Błaszczak	karolina.blaszczak@onet.pl
Paulina Przybysz	paulinaprzybysz.01@gmail.com
Monika Szyszka	monika.szyszka@onet.com.pl
Maja Kucharska	maja.kucharska30@gmail.com

ORCID List

Natalia Paduszyńska	0000-0001-9953-662X
Anna Dąbrowska	0009-0003-2289-5909
Adrian Kruszewski	0009-0003-6077-4948
Karolina Błaszczak	0009-0000-1534-6977
Paulina Przybysz	0009-0004-8141-2409
Monika Szyszka	0009-0005-5054-4465
Maja Kucharska	0009-0006-4599-8654

Peer-Review History
Received: 10 April 2024
Reviewed & Revised: 13/April/2024 to 21/June/2024
Accepted: 25 June 2024
Published: 03 July 2024

Peer-review Method
External peer-review was done through double-blind method.

Medical Science
pISSN 2321–7359; eISSN 2321–7367

DISCOVERY SCIENTIFIC SOCIETY

Therapeutic strategies in Uveal Melanoma: A comprehensive review of primary and metastatic disease treatment approaches

Natalia Paduszyńska[1*], Anna Dąbrowska[1], Adrian Kruszewski[1], Karolina Błaszczak[1], Paulina Przybysz[2], Monika Szyszka[3], Maja Kucharska[3]

ABSTRACT

Uveal melanoma (UM) is a sparse tumor situated inside the eyeball. It occurs more often in adults but can appear also in children. The location of the neoplasm, which implies difficulties in access, the severe course of the disease, and unfavorable prognosis for patients, especially in an advanced stage of the disease, make uveal melanoma a medical challenge. Therefore, early detection of a lesion and immediate treatment are so significant. Available methods include conservative and surgical ones. Primary tumor therapy includes radiotherapy, surgical resection, photocoagulation, transpupillary thermotherapy, and photodynamic therapy. In turn, treatment of metastases, most often affecting the liver, involves: Metastasectomy, radio-, immuno- and chemoembolisation, isolated or percutaneous hepatic perfusion, and molecular targeted therapy. The last mentioned is a developing and promising field of study. A breakthrough step in recent years was the registration of tabentafusp, the first monoclonal antibody and the first molecule for the therapy of metastatic disease. This article summarizes crucial information regarding currently implemented therapeutical approaches, novel molecules, and solutions that are the subject of research.

Keywords: Uveal melanoma; primary tumor; metastasis; treatment; tabentafusp

1. INTRODUCTION

Uveal melanoma is the most prevalent malignant lesion detected inside the eyeball in adults. It involves the choroid, ciliary body, or iris. The metastatic disease affects approximately fifty percent of patients and the most common localization of metastasis is the liver. The disseminated disease is characterized by significantly reduced survival. Thus, the therapy of primary tumors is crucial. The local treatment prevents recurrences with an effectiveness of 85%, and the

frequency of metastases within 20 years after such treatment ranges from 20 to 70%, depending on the tumor stage at diagnosis (Rao et al., 2020). The main treatment methods available in uveal melanoma contain radical and conservative approaches.

Selecting the appropriate therapeutic path is a multi-stage process. It is necessary to consider many factors such as tumor size and extent, status of opposite eye, patient age, psychological status, and general health. However, the most essential assumption of therapy is to strive for tumor removal while preserving vision and preventing metastatic disease (Shields and Shields, 2015). Due to the poor prognosis and still-developing treatment methods, managing a patient with uveal melanoma is demanding. Only one drug has been registered for the treatment of metastatic disease so far. Therefore, in this article, we would like to summarize significant and clinically necessary information regarding available treatment and highlight the molecules that are the subject of research.

2. MATERIAL AND SEARCHING METHOD

This paper analyzes the literature in PubMed and Google Scholar scientific databases for the years 2006-2024 regarding uveal melanoma, primary tumor, metastatic disease, treatment, and tabentafusp.

3. RESULTS AND DISCUSSION

Treatment of primary tumor

If the detected lesion presents features atypical of UM, close serial observation is recommended. It is preferred also when the patient's condition precludes the other treatment methods due to advanced age or serious diseases. If during observation the detected lesion has no potential for growth, infiltration of adjacent tissues, or metastasis, observation is preferable to the other methods, because it allows avoiding unnecessary interventions, tedious treatment, and its consequences (Chattopadhyay et al., 2016). Currently, regular control using fundus photography is preferred until the tumor grows or factors heralding malignant transformation (greater thickness, subretinal fluid, symptoms, orange pigment, margin, ultrasonographic hollowness, halo absence) occur, then treatment is necessary (Shields et al., 2018).

Radiotherapy

Radiotherapy (RT) is a first-line widely used therapeutic tool, especially in posterior uveal melanoma (Singh et al., 2011). The following types are distinguished: Plaque brachytherapy (using iodine-125, I-125; ruthenium-106, Ru-106; palladium-103, Pd-103; or cobalt-60, Co-60), teletherapy, including proton beam and helium ion, and stereotactic radiotherapy (SRT), including a cyber knife, gamma knife, and linear accelerator (Kaliki and Shields, 2017). This division results from differences in the location of the radiation source. In brachytherapy, a radioisotope is placed on the surface or interior of the tumor, while in teletherapy the radiation derives from a source situated outside the patient. In turn, SRT involves the emission of a fractionated radiation beam from several different directions toward the tumor while sparing the surrounding tissues (Tarlan and Kıratlı, 2016).

In the USA, I-125 is applied more often, and in Europe Ru-106. Proton beam, also charged particle radiation, is not available in all centers, but constitutes an alternative to plaque brachytherapy in terms of treatment results, and limits tumor development and prognosis for patients (Gragoudas, 2006). Similarly, when it comes to comparing photon beams and SRT, it turns out both methods are analogous regarding local tumor control, visual outcome, and patient survival (Dunavoelgyi et al., 2011). Radiotherapy, as an eye-preserving method, is used especially in patients with limited uveal melanoma while the larger tumor size predisposes the choice of surgical treatment. Tumors measuring ≤18 mm in diameter and ≤12 mm in thickness are subjected to plaque RT (Rao et al., 2017).

Study results comparing the effectiveness of eye-sparing RT and enucleation indicate similar effectiveness of both methods in reducing the risk of mortality and metastasis (Mosci et al., 2012). In turn, the proton beam RT in the case of iris melanoma allows for the reduction of the need for iridectomy (Konstantinidis et al., 2013). Generally, the most convenient outcomes of treatment with a proton beam concern small tumors not extending close to the optic disc and fovea (Mishra and Daftari, 2016). Although RT serves as a prevalent therapeutic tool, the range of complications it may cause is quite wide. In most cases, their occurrence depends on the dose of radiation the patient received.

The complications include radiation retinopathy, maculopathy, optic neuropathy, scleral necrosis, hemorrhage, cataract, macular edema, retinal detachment, or neovascular glaucoma (Jager et al., 2020; Seregard et al., 2013). There was also mentioned toxic tumor

syndrome after irradiation of uveal melanoma. Necrosis resulting from radiation causes inflammation, retinal edema, posterior synechia, cataracts, and neovascular glaucoma. In such circumstances, even enucleation may be necessary (Konstantinidis et al., 2014).

Surgical treatment

Surgical methods are reserved for advanced tumors. Among patients with uveal melanoma, 20-40% require such a procedure. Based on the extent of conducted procedures, the following are distinguished: local resection, uvectomy – selective removal of anterior uveal tract tumors such as iris melanoma, enucleation – extraction of the globe, exenteration – removal of an eye and ambient tissue, which is performed extremely rare, only in the case of extensive orbital invasion. The local resection options include exoresection (tumor removal via the transscleral route) and endoresection (tumor resection via the transretinal route). Applying plaque RT as an adjuvant after exoresection could be effective in preventing recurrence (Damato, 2012).

The resection methods mentioned above pose a risk of complications such as hemorrhage, retinal detachment, ocular hypertension, and proliferative vitreoretinopathy (Damato, 2012). Local resection is not the first-choice method, instead, RT is favorable as a conservative treatment approach. However, in the case of large tumors unsuitable for brachytherapy, enucleation is more appropriate. Enucleation is dedicated to advanced tumors with thickness>12mm, and diameter>20mm, when the optic nerve is involved, with extrascleral extension and secondary glaucoma (Dogrusöz et al., 2017). The advantage of all surgical methods is the obtaining of tissue for histopathological examination to confirm the diagnosis and assess prognosis ultimately (Damato, 2006).

Laser treatment

Laser treatment of ocular tumors consists of photocoagulation, transpupillary thermotherapy (TTT), and photodynamic therapy (PDT). Photocoagulation is of limited importance, especially in centers with available radiotherapy. This method may be functional in treating small tumors but increases the risk of retinal traction, gliosis, and tumor recurrence (Souto et al., 2019). In turn, TTT applies an infrared laser beam directed toward the tumor through the pupil. This technique applies the thermal destruction of pathological tumor blood vessels. The utility of this method focuses on small choroidal melanomas because the penetration depth is 4mm. The most significant advantage is achieved by patients with tumors under 3 mm in thickness and situated over 3 mm away from the fovea (Dogrusöz et al., 2017). A study that analyzed 391 patients with UM undergoing TTT revealed the recurrence rate of 5 years was 29% (Mashayekhi et al., 2015).

In turn, PDT leads to the destruction of tumor cells and vascularization and triggers a local inflammatory process resulting in autophagy. First, it is necessary to administer the photosensitizer-verteporfin, which accumulates in the tissues intravenously, and then it is activated using a laser. Melanin may interfere with the process; therefore, pigmented tumor is a contraindication to therapy. This method is preferable for amelanotic melanomas with <4 mm in thickness (Cerman and Çekiç, 2015). Among 12 choroidal melanomas treated with PDT, 67% of cases were under control, and 33% had recurrence (Turkoglu et al., 2019). A novel infrared dye-conjugates virus-like nanoparticle (AU-011) is under investigation to introduce it to regular therapy for small choroidal melanoma. That particle presents a tropism for proteoglycans found on melanoma cells. The administration of this molecule in intravitreal injection into suprachoroidal space enables the achievement of appropriate concentration. Upon photoactivation, the molecule induces cell membrane disruption and cancer cell necrosis.

Treatment of metastatic disease

Response rates of metastatic disease treatment are poor, and prolonged survival is only a few months (Khoja et al., 2019). Only one drug has been registered in systemic therapy for metastatic UM so far, and further research is required to develop new therapies and clear standards of practice. Admittedly, the results of treatment UM using drugs implemented in cutaneous melanoma are worse. Therefore, experts recommend qualifying patients for clinical trials (Barker and Salama, 2018). The early detection of the lesion's metastatic potential is crucial due to an unfavorable prognosis for disseminated disease and the limited effectiveness of therapy. Genomic testing serves this purpose. The risk stratification takes into account the following factors: BAP1 (breast cancer-associated protein 1) mutation, the status of chromosomes 3, 5, and 8, tumor stage, ciliary body involvement, extraocular extension, and spindle versus epithelioid cell type. Such research facilitates deciding whether the patient requires observation or participation in a clinical trial (Barker and Salama, 2018).

Chemotherapy

The range of chemotherapeutical agents studied in systemic UM is extensive. Research including dacarbazine, treosulfan, temozolomide, cisplatin, or fotemustin, both individually and in combinations, did not reveal any satisfactory results (Carvajal et al., 2017). Similarly, the modified molecules, such as docosahexaenoic acid–paclitaxel and vincristine sulfate liposome infusion, were not effective. Therefore, systemic cytotoxic therapy is not implemented in the therapeutic process (Pereira et al., 2013).

Adjuvant and molecular targeted therapy

A potential opportunity to increase patient survival is adjuvant therapy. It comprises radiotherapy or systemic treatment - immunotherapy or chemotherapy, and targeted therapy. The method aims to target micrometastases, indicated by the presence of cancer cells circulating in the blood at the time of diagnosis (Bidard et al., 2014). One study referred to patients with UM treated with interferon-α in two single-arm trials compared with historical controls, but no survival benefit was admitted (Lane et al., 2009). The randomized study on the methanol-extracted residue of Bacille Calmette-Guerin (BCG) revealed no survival advantage (Stewart and Levine, 2011). Fotemustine was investigated by intraarterial hepatic chemotherapy. Although a trend toward increased survival occurred, it did not reach statistical significance (Leyvraz et al., 2014).

A phase 3 multicenter randomized trial of adjuvant fotemustin (FOTEADJ), following genomic analysis, was terminated early due to slow participant enrollment (Piperno-Neumann et al., 2017). Ongoing clinical trials focus on drugs and particles, taking into account specificity and pathogenetic processes underlying UM. Some of the agents, such as selumetinib and trametinib, target overactive signal transmission pathways – MEK (mitogen-activated protein kinase) and PKC (protein kinase C) in the tumor cells, which result from GNAQ/GNAS (guanine nucleotide-binding protein Gq/guanine nucleotide-binding protein G alpha stimulating) mutation. A multicenter randomized trial of selumetinib (SUMIT) reported no significant difference in progression-free survival (PFS) between interventions of selumetinib plus dacarbazine and dacarbazine alone (Carvajal et al., 2018).

In the 1 phase study of trametinib, UM patients revealed no significant response (Falchook et al., 2012). Another particle overexpressed in UM as a therapeutic target is c-kit – the transmembrane receptor with tyrosine kinase activity. Imatinib, a c-kit inhibitor, demonstrated tumor-limiting properties in vivo. However, further studies revealed a lack of effectiveness in UM (Penel et al., 2008). Sunitinib, a c-kit inhibitor, was used in a retrospective study, which revealed better overall survival (OS) (Valsecchi et al., 2018). Cabozantinib acts as a multikinase inhibitor because it blocks tyrosine kinases, c-Met kinase, and vascular endothelial growth factor receptor-2 (VEGFR2). In a randomized controlled study, compared to cabozantinib and dacarbazine or temozolomide, no improvement in PFS in patients with metastatic UM treated with cabozantinib was reported (Luke et al., 2020).

In turn, crizotinib is a monoclonal antibody and inhibitor of ALK (anaplastic lymphoma kinase) and ROS1 (ROS proto-oncogene 1). In a murine model, it reduced the development of distant metastases of UM (Surriga et al., 2013). However, a recent study of crizotinib administered to high-risk patients did not result in improved PFS compared to historical controls (Khan et al., 2022). Another therapeutic target is to block the process of angiogenesis, which is crucial for neoplasm progression. Therefore, the particles under investigation target vascular endothelial growth factor (VEGF), a pivotal cytokine that promotes vascular formation. VEGF inhibitors include bevacizumab and aflibercept. Although the initial results for both molecules in metastatic UM therapy were promising, further evaluation is warranted (Piperno-Neumann et al., 2013, Spitler et al., 2015).

In turn, sorafenib – an inhibitor of kinase RAF/MEK/ERK (rapidly accelerated fibrosarcoma/mitogen-activated kinase/extracellular signal-regulated kinase) pathway and VEGF/PDGFR (vascular endothelial growth factor /platelet-derived growth factor receptor), was investigated in combination with carboplatin and paclitaxel in metastatic UM, and the overall efficiency did not warrant further clinical testing (Bhatia et al., 2012). Understanding genetic mechanisms underlying UM development has prompted further research into epigenetic processes. One of the most common genetic abnormalities involves the loss of BAP1-suppressor, which affects the degree of gene expression by accumulation of ubiquitin on histone-H2A and promotion of de-differentiated cellular phenotype. Histone deacetylase inhibitors (HDACis) such as valproic acid might present therapeutic properties by promoting differentiation and extending the dormancy of micrometastatic disease in UM (Fagone et al., 2017).

The eye characterizes immunological privilege, and the immunosuppressive particles occur in the aqueous humor. Cancer cells exploit this condition and develop new strategies to avoid recognition and elimination by the host's immune system. These include the expression of immunosuppressive particles, which inhibit T lymphocytes or natural killers (NK) cells, complement inactivation, and induction of T cell apoptosis via PD-L1 (programmed death ligand-1) (Kummer and Schuler-Thurner, 2017). Therefore, research aims to

identify agents that influence immune reactions. One study revealed that adjuvant dendritic cell (DC) vaccination potently enhances the host's antitumor immunity against UM and may be associated with prolonged survival in patients with metastatic UM. The other is an ongoing phase I trial that investigates mRNA-transfected DCs vaccine, which primes T cells and NK cells (Koch et al., 2022).

Immune checkpoints are the subject of research on subsequent molecules. Monoclonal antibodies targeting PD1 (programmed cell death 1 protein) improved the results in patients with metastatic cutaneous melanoma. However, in UM, the results are not so optimistic (Seth et al., 2020). Among the molecules that affect T lymphocytes, we can distinguish pembrolizumab or nivolumab directed against PD-1 protein, durvalumab or atezolizumab directed against PD-L1(programmed cell death ligand 1), and ipilimumab directed against CTLA-4 (cytotoxic T-lymphocyte associated antigen). Their effectiveness in UM measured by response rates was <10% and the median survival was <1 year (Oliva et al., 2016). However, patients with germline mutation-MBD4 (methyl-CpG binding domain 4) may benefit from blocking PD-1(Rodrigues et al., 2018). The efficiency of pembrolizumab with etinostat is under investigation in a phase II study in adult patients with UM (PEMDAC study) (Jespersen et al., 2019).

A phase II study of a combination of nivolumab and ipilimumab in patients with metastatic UM demonstrates activity, with deep and sustained confirmed responses (Pelster et al., 2021). A notable molecule deserving of attention is tabentafusp (IMCgp100), which received its first approval for treatment of UM in the USA in January 2022. In February 2022, it obtained a Positive Opinion from the EU Committee for Medicinal Products for Human Use. The registration includes treating unresectable or metastatic disease in adult patients who are positive for HLA-A*02:01 (Dhillon, 2022). Tabentafusp is a first-in-class immune-mobilizing monoclonal T cell receptor against cancer (ImmTAC). This molecule can bind to human leukocyte antigen attached to the cell via glycoprotein 100 (gp100) - highly expressed on neoplastic cells, and engage T cells by anti-CD3 single chain antibody fragment (scFv), which results in the release of inflammatory cytokines and cytolytic substances causing tumor cells lysis (Chen and Carvajal, 2022).

Surgical treatment

A recent meta-analysis in metastatic uveal melanoma evaluating progression-free and overall survival benchmarks revealed that patients treated with liver-directed treatments had statistically significant longer PFS and OS (Khoja et al., 2019). Targeted therapy includes resection, embolization, hepatic perfusion, and thermotherapy. Surgical resection involves the removal of metastatic nodules but is applicable in selective cases. Although surgery patients achieved prolonged survival, this benefit concerned a narrow group of candidates. Patients scheduled for surgery must meet the resection criteria, which involve approximately 10% of patients. The presence of multiple metastases constitutes a contraindication. The length of overall survival depends on the degree of respectability. However, the median OS after surgical treatment was 17 months (Rantala et al., 2019). Nevertheless, more optimistic long-term survival results concern the combination of surgery and chemotherapy. Combining metastasectomy and hepatic-targeted therapy has shown potential to prolong survival in certain cases.

Embolization

The fact that the hepatic parenchyma is mostly vascularized by the portal vein, while tumors are supplied by the hepatic artery, has been used as a therapeutic target. Chemoembolization involves the intra-arterial administration of a chemotherapeutic agent and embolization of the vessel. This procedure aims to cut the tumor off the blood supply and leave the drug in the area of the tumor for a longer time. One of the investigated agents is BCUN (1,3-bis(2-chloroethyl)- 1-nitrosourea) (Gonsalves et al., 2015). The other chemotherapeutics include cisplatin or fotemustine. The median OS achieved by TACE was 10 months (Rantala et al., 2019). Immunoembolization (IE) involves the intra-arterial injection of an immunostimulating agent and vascular occlusion.

Application of granulocyte-macrophage colony-stimulating factor (GM-CSF) assumes mobilization of dendritic cells and their recruitment towards the tumor that has undergone necrosis as a result of embolization. A phase I trial revealed a response rate of 33% (Sato et al., 2008). However, a phase II trial did not show longer survival. Radioembolization (RE), also known as SIRT–selective internal radiation therapy, using the radiospheres with yttrium 90 (90Y) isotope, aims to deliver an appropriate dose of cell-destroying radiation to the tumor area while occluding the artery. The tissue penetration of radiation oscillates between 2 to 4 mm, which allows for sparing the tissues surrounding the tumor (Eschelman et al., 2013).

A prospective phase II trial of RE for the treatment of UM hepatic metastasis compared treatment-naïve participants and patients who progressed after immunoembolization and the median OS of 18.5 months and 5.2 months, respectively (Gonsalves et al., 2019).

Other studies revealed prolonged OS, but the difference in small series was inconclusive. In turn, in the meta-analysis, the median OS in patients undergoing RE was 11,3 months (Rantala et al., 2019).

Hepatic perfusion

Isolated hepatic perfusion (IHP) involves a surgical method where the liver is isolated and perfused with high doses of chemotherapeutics through the hepatic artery and vein. This approach allows for the avoidance of systemic side effects of chemotherapy. Some studies evaluating IHP in metastatic UM reported a decrease in 1-month mortality from 7% to 2% (Ben-Shabat et al., 2016). An alternative method is percutaneous intrahepatic perfusion (PHP). This technique involves the hepatic artery administering the chemotherapy, the inferior vena cava receiving blood from the liver, and the right jugular vein returning blood filtered outside the patient. Studies concerned with PHP with melphalan in UM revealed significantly improved median PFS compared with alternative treatment care (Karydis et al., 2018). Progression-free survival in patients treated with PHP is 3,1 months based on a randomized study FOCUS 301.

Ablation

The treatment options for UM liver metastases include thermal destruction methods such as radio-frequency ablation (RFA) or laser ablation. Studies assessing the efficacy of thermotherapy in these lesions have shown overall survival ranging from 29 to 38 months. However, additional prospective trials are needed to thoroughly evaluate the effectiveness of ablation (Bale et al., 2016).

3. CONCLUSION

An unfavorable UM prognosis poses a significant therapeutic challenge for both primary and disseminated disease. Certainly, treatment options still necessitate additional research, as currently, only one drug has been approved for metastatic disease. Developing new molecules that would be a component of personalized medicine is crucial to achieving improved survival outcomes.

Author's Contribution

Natalia Paduszyńska: Conceptualization, writing- rough preparation, methodology, investigation
Anna Dąbrowska: Conceptualization, methodology
Adrian Kruszewski: Formal analysis, supervision
Karolina Błaszczak: Visualization, data curation
Paulina Przybysz: Conceptualization, writing- rough preparation
Monika Szyszka: Methodology, data curation
Maja Kucharska: Writing - Review and editing, supervision

Ethical approval

Not applicable.

Informed consent

Not applicable.

Funding

This study has not received any external funding.

Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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